Prevention of endpoints in primary biliary cholangitis with ursodeoxycholic acid: quantifying the benefit

Jörn M Schattenberg

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with an established benefit for patients suffering from primary biliary cholangitis (PBC). It was first introduced in the 60s and took until the late 90s to demonstrate a survival benefit in large meta-cohort studies.[1] Since then, UDCA is the established first-line therapy according to current guidelines.[2] The benefit of UDCA is multidimensional, and patients receiving UDCA experience increased transplant-free survival, a decreased risk of hepatocellular carcinoma and potentially improved quality of life.[3–5] The survival benefit is predicted by a number biochemical markers that reflect cholestasis and that are accepted surrogates of the treatment response—a fact that has accelerated drug development and approval. Interestingly, even patients who are considered incomplete responders to UDCA—characterised by persistently elevated alkaline phosphates levels (ALPs) or abnormal bilirubin—a survival benefit compared with patients that are not on UDCA can be detected.[4] The mechanism by which UDCA mediates these effects are numerous and involve: (1) protection of chonlangiocytes from cytotoxic hydrophobic bile acids, (2) increased hepatobiliary secretion of bile components and (3) protection of hepatocytes from bile acid-induced apoptosis. UDCA enrichment in the bile is linear to the administered dose and thus a sufficient dose—typically ranging between 13 mg/kg and 15 mg/kg bodyweight—is required to achieve therapeutic efficacy. The safety profile of UDCA is positive with only few patients experiencing dyspepsia, lose stools or mild diarrhoea. Therefore, all patients diagnosed with PBC according to current criteria should be started on UDCA as primary treatment immediately.

More recently, second-line therapies—including bezafibrate and the steroidal FXR-agonist obeticholic acid (OCA)—have been trialled in patients with an incomplete treatment response to UDCA. It is important to note that these patients experience an excess of clinically relevant endpoints and therefore are at need of additional therapy. In the respective pivotal trials, the addition of these drugs to UDCA lead to an incremental treatment response according to the particular endpoint of 31% for bezafibrate at 2 years and 47% for OCA at 1 year.[6 7] Importantly, these drugs also introduce additional side effects with pruritus and low density lipoprotein (LDL) cholesterol elevations occurring from OCA and increased serum creatinine and myalgia from bezafibrate.[6 7] Nonetheless, based on the prognostic relevance of persistently elevated ALP and/or bilirubin levels in patients with PBC, these adjunctive therapies are needed in a subset of patients with PBC.

In order to quantify and support the benefit from UDCA, Harms and colleagues[8] explored the number-needed to treat (NNT) with UDCA to prevent adverse outcome in PBC in an article published in *Gut*. The authors used the large and well-characterised Global PBC Study Group database to calculate the NNT at 5 years and 10 years (NNT 5y/10y) in order to prevent one liver transplantation or death. The study included a total of 3902 patients with a median follow-up time of 7.8 years from this unique cohort. Only 59.1% of the patients achieved an optimal biochemical response to UDCA with ALP <1.67×upper limit of normal (ULN) at 1 year. The corresponding 5-year and 10-year liver transplantation- -free survival rates were 94.0% and 84.7% in this group. In contrast, patients with an ALP >1.67 ULN exhibited 88.0% and 70.9% LT-free survival rates at 5 years and 10 years. These data highlight one of the peculiarities of the Global PBC Study Group cohort that comprises a fairly 'difficult' to treat patient population recruited at the highly experienced PBC centres across Europe, Canada and the USA. In a recent monocentric analysis at a German tertiary referral and transplant centre, the rate of complete biochemical response (defined as ALP <1.67 ULN and bilirubin ≤ULN) at 1 year was 76%.[5]

The current study by Harms *et al* reports an HR of 0.46 for UDCA use when compared with patients not on UDCA and 90.5% of the entire cohort received UDCA.[8] In patients not on UDCA, the historic 5-year LT-free survival rate was 81% and based on this the NNT to prevent one LT or death within 5 years was 11. Unfortunately, the retrospective nature of the analysis did not allow to assess why UDCA was not prescribed—a

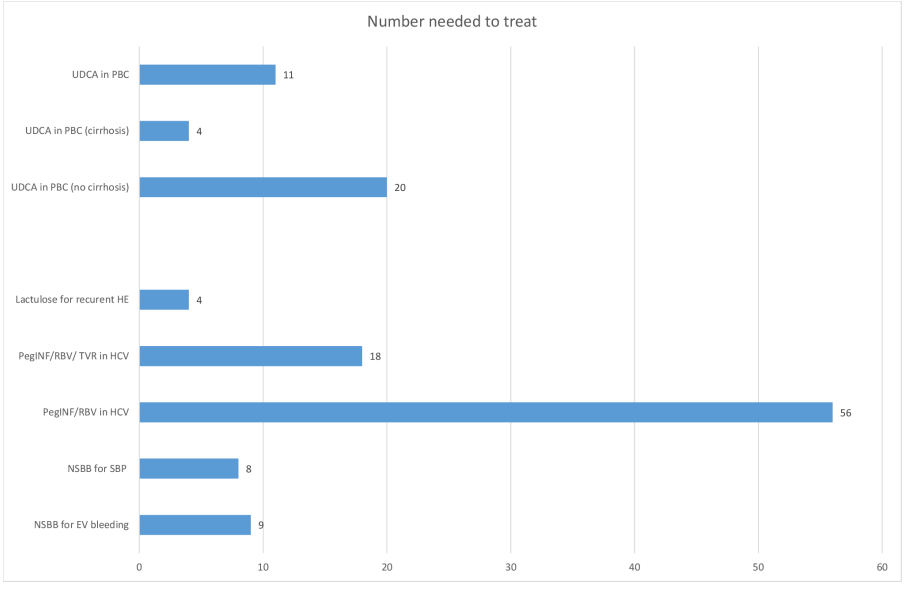

Figure 1 Number-needed-to-treat to prevent endpoints across different liver disease according to the different studies.[8–13] EV. esophageal varices; HE, hepatic encephalopathy; NSBB, non-selective beta blocker; PBC, primary biliary cholangitis; PegINF, PEGylated interferon; RBV, ribavirin; SBP. spontaneous bacterial peritonitis: TVR, telaprevir; UDCA, ursodeoxycholic acid.

Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Correspondence to Prof. Dr. Jörn M Schattenberg, I. Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz 55131, Germany; joern.schattenberg@unimedizin-mainz.de

clinical decisions or patient's preferences have to be assumed. Nonetheless, these data are a strong argument supporting the use of UDCA and quantify the clinical benefit for the first time allowing for biomedical and statistical assessment in this orphan disease. Interestingly, the HR was comparable for patients with and without cirrhosis. On the other side, the NNT to prevent one clinically relevant endpoint was significantly higher in non-cirrhotic patients (NNT at 5y: 20) when compared with cirrhotic patients (NNT at 5y: 4; see figure 1). Also, the clinical efficacy was higher in patients with ALP >4× ULN (NNT at 5y: 5) compared with benefit in patients with ALP ≤2× ULN (NNT at 5y: 26) figure 1 Considering the overall favourable safety profile of UDCA, these numbers propagate and underline the recommendation to initiate treatment in patients diagnosed with PBC immediately. As a matter of fact, the NNT declined with increasing treatment duration. This recommendation is particularly true when considering that second-line therapies exhibit a less favourable safety profile.

To place the reported NNT for UDCA at 5 years in PBC into context, it can be compared with what has been reported in other liver disease (figure 1). Robust data exist for the use of beta blockers in the prevention of a first bleeding in cirrhotic patients in a high-risk category. In a meta-analysis pooling data of nine trials, an NNT between 9 and 11 was reported across different time points.[9] Comparably, a meta-analysis observed an NNT of 8 in preventing one additional episode of spontaneous bacterial peritonitis in cirrhosis.[10] An even lower NNT has been observed for lactulose in the prevention of recurrent hepatic encephalopathy coming down to 4 over up to 20 months of follow-up.[11] Higher NNTs were reported for less effective therapies including for peg-interferon, ribavirin and telaprevir (NNT: 18)[12] and peg-interferon and ribavirin (NNT: 56) in chronic hepatitis C infection.[13] It is important to note that the above detailed numbers do not necessarily reflect the superiority of one treatment concept over another. In particular when the cure from a viral infection is weighted against the control of a chronic condition that can impact quality of life independent of the endpoint accounted for in the NNT concept. Additionally, the NNT across different indications is reflecting different treatment and study durations further limiting a direct comparison. Nonetheless, the study by Harms *et al* is remarkable for three reasons: (1) quantification of the clinical benefit supports treatment decisions in this orphan disease, even outside of expert centres. (2) The NNT—in particular in advanced disease and incomplete responders—underlines the value of UDCA as a first-line therapeutic option for the treatment of PBC. From personal experience, the number of patients reporting an intolerance to UDCA is low, and they can be coached in order to increase the acceptance and potentially overcome this 'intolerance' thereby maximising the clinical benefit of first line treatment. (3) With the availability of second-line therapies, the published data are a useful tool to assess the additional benefit of second-line therapies from a health economic perspective in the subgroup of patients irresponsive to UDCA.

Twitter Jörn M Schattenberg @schattenbergj

Contributors This is my sole work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JMS has acted as consultant to Intercept Pharmaceuticals, Genfit, Gilead Sciences, Novartis, Echosens, Pfizer, Roche and Siemens Healthineers and has received Research Funding from Gilead Sciences.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Schattenberg JM. *Gut* 2020;**69**:1377–1378.

Received 5 January 2020
Revised 6 March 2020
Accepted 8 March 2020
Published Online First 23 March 2020

Linked

► http://dx.doi.org/10.1136/gutjnl-2019-319057

Gut 2020;**69**:1377–1378.
doi:10.1136/gutjnl-2019-320355

ORCID iD
Jörn M Schattenberg http://orcid.org/0000-0002-4224-4703

REFERENCES

1 Poupon RE, Lindor KD, Cauch-Dudek K, *et al*. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997;113:884–90.
2 EAftSot L. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;67:145–72.
3 Trivedi PJ, Lammers WJ, van Buuren HR, *et al*. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016;65:321–9.
4 Harms MH, van Buuren HR, Corpechot C, *et al*. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. *J Hepatol* 2019;71:357–65.
5 Kaps L, Grambihler A, Yemane B, *et al*. Symptom burden and treatment response in patients with primary biliary cholangitis (pBC). *Dig Dis Sci* 2019;8.
6 Corpechot C, Chazouillères O, Rousseau A, *et al*. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018;378:2171–81.
7 Nevens F, Andreone P, Mazzella G, *et al*. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016;375:631–43.
8 Harms MH, de Veer RC, Lammers WJ, *et al*. Number needed to treat with ursodeoxycholic acid therapy to prevent liver transplantation or death in primary biliary cholangitis. *Gut* 2020;69:1502–9.
9 Pagliaro L, D'Amico G, Sörensen TI, *et al*. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. *Ann Intern Med* 1992;117:59–70.
10 Senzolo M, Cholongitas E, Burra P, *et al*. β-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009;29:1189–93.
11 Sharma BC, Sharma P, Agrawal A, *et al*. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology* 2009;137:885–91.
12 Rowe IA, Houlihan DD, Mutimer DJ. Despite poor interferon response in advanced hepatitis C virus infection, models of protease inhibitor treatment predict maximum treatment benefit. *Aliment Pharmacol Ther* 2012;36:670–9.
13 van der Meer AJ, Veldt BJ, Feld JJ, *et al*. The number needed to treat to prevent mortality and cirrhosis-related complications among patients with cirrhosis and HCV genotype 1 infection. *J Viral Hepat* 2014;21:568–77.